ORIGINAL ARTICLE

# Clinical efficacy of diazepam after whiplash: a randomized controlled study

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## ABSTRACT

**Aim** To investigate the role of short-term diazepam therapy for improving long-term outcomes and reducing neck pain after whiplash injury.

**Methods** A total of 89 patients suffering from whiplash injury were included. They were randomly assigned into 2 groups: group A (study group), and group B (control group). The test group was prescribed with diazepam 5 mg tablets one time per day for 7 days and the control group did not get the recommendation to use diazepam. Three previously validated scales, Visual Analogue Pain Scale (VAS), the Neck Disability Index (NDI), and the Whiplash Disability Questionnaire (WDQ), were used at different intervals (7 days, 6 weeks and 6 months after the injury).

**Results** Among 89 patients, 50 (56.2%) were males, 39 (43.8%) females. The mean age of all participants was 34.80±12.531 years. According to the Mann Whitney U –Test, no significant difference was observed in VAS, NDI, and WDQ scores between the control group and study group at any time point ($p>0.05$).

**Conclusion** Diazepam provides no substantial advantage in the treatment of whiplash, and accordingly, we do not recommend diazepam therapy in patients who suffered whiplash injury.

The trial was registered in the database of the Federal National Library of Medicine (NLM) (https://clinicaltrials.gov) under clinical trials (unique protocol ID:1703016).

**Key words:** neck pain, pain measurement, spasm

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## INTRODUCTION

Whiplash is defined as an injury of bone or soft tissues caused by acceleration-deceleration of energy transfer to the neck (1). It is usually associated with rear-end car accidents; the collision results in quick forward and backward movement of individual's head and body, which causes neck stretching (2). Whiplash injury can also be caused by sport injuries, physical abuse, or other similar trauma (3). In a rear-end collision, the chest is thrust forward, causing rapid hyperextension and tension of the lower cervical spine followed by flexion of the upper cervical spine, resulting in an "S" shape spine.

Whiplash injury is associated with multiple symptoms depending on its severity. The common neurological symptoms include headache, memory impairment, temporomandibular joint dislocation, sleep disturbances, anxiety, stress, dizziness, vestibular dysfunction, blurred vision, paraesthesia, etc. (3-5).

The diagnosis of this injury is primarily clinical. Headache is reported in almost 70% of patients and is associated with the movement of the neck. Moreover, exhaustion, anxiety, insomnia may also trigger headaches (6,7). Neck pain is reported in 65% of patients within 6 hours of the onset of the injury. Within a day, 93% of patients report neck pain, and 100% of patients within three days (8). The delay in neck pain is caused by the facet joint synovitis, which occurs when the synovial tissue of the facet joint is damaged due to nonphysiological activity after a collision (6). The recovery process is long and it takes up to three months to recover from the pain, but studies have reported that pain persists for years in 25% of the cases (9,10). Approximately half of the patients experience persistent or residual symptoms (such as neck discomfort, headache, and activity limitations) for an extended period of time after the injury. The most consistent prognostic variables for extended activity limitations and participation issues are high pain intensity and pain-related impairment (11,12).

In most countries, the incidence and prevalence of traffic-related whiplash have increased. In North America and Western Europe, the annual incidence is estimated to at least 300/100,000 population (13). Estimated annual incidence of whiplash-associated disorders (WAD) in the UK is around 300,000/ (14). A recent study in Japan reported the prevalence of around 8% in males and nearly 10% in females. Whiplash injuries with symptoms lasting longer than three months were reported by 34.3% in males and 24.2% in females (15).

Whiplash injuries impose a substantial financial strain on the patient, the healthcare system and insurance sectors. The annual economic cost of WAD is projected to be $3.9 billion in the United States (16) and €10 billion in Europe, with insurance claims rising from £7 to £14 billion in a decade (17,18).

In whiplash injury muscular spasms and pain are inextricably linked. The initial injury is believed to cause a reflex spasm of the affected muscles. Moreover, studies have reported that many doctors prescribe muscle relaxants with analgesics and anti-inflammatory agents (19). Furthermore, studies have shown promising results when muscle relaxants were prescribed with NSAIDs or other drugs against pain (20).

In the current study, we investigated the role of diazepam on the long-term outcome of whiplash injury. Diazepam is an anxiolytic that is used to treat anxiety and insomnia. It can also be used to treat muscle spasms, because of the positive effect by causing muscle relaxation (21). To our knowledge, there are no published studies investigating the effect of diazepam on the long-term outcome of whiplash injury.

The aim of this study was to determine whether short-term diazepam therapy after whiplash injury positively affects the long-term outcome measuring changes in the neck disability index using the Whiplash Disability Questionnaire, and Visual Analogue Pain Scale (VAS) scale 7 days, 6 weeks, and 6 months after the motor vehicle accident.

## PATIENTS AND METHODS

### Patients and study design

This randomized, assessor-blinded study was conducted on patients presented to the Emergency Department of the Cantonal Hospital "dr. Safet Mujić" Mostar, Bosnia and Herzegovina, due to a cervical spine injury caused by a traffic accident in the previous 48 hours in the period between 1 January 2020 and 31 December 2020.

The sample size was determined by the number of cases in an earlier period in this area. It was considered necessary to include 30 patients per group to facilitate the detection of 50% difference in pain level (type I error frequency: 0.05, power: 0.80).

Inclusion criteria were patients between 18 to 70 years of age who had suffered a cervical spine injury in a traffic accident in the previous 48 hours. Exclusion criteria were patients under the age of 18 and over the age of 70, additional injuries of other body parts, previous cervical spine surgery, previously diagnosed cervical spine arthrosis, a malignant process, history of cervical spine injuries, and diazepam allergy.

The Ethics Committee of the Cantonal Hospital "dr. Safet Mujić" Mostar approved the study (ERC NO 02-6-1-4349), and to the best of our knowledge, all study methods were carried out following the Declaration of Helsinki's ethical guidelines. The trial was registered in the database of the Federal Clinical Trials (unique protocol ID:1703016). In this study, the patients' participation was voluntary, and all the participants signed a written consent.

**Randomization**. The patients were divided into two groups: group A (study group), and group B (control group). In order to ensure approximately the same number of patients in both groups, 50 blank papers with the inscription "Group A" and 50 with the inscription "Group B" were printed, and were separately inserted into opaque white envelopes, which were then sealed and placed in a large box. After signing the consent to participate in the study, the patients were asked to select one sealed envelope from the box and to open it, read the text from the paper. The patients who received "Group A" were assigned in the test group, while the patients with "Group B" paper were assigned to the control group.

**Initial assessment**. During the initial examination after the injury, detailed patient history was taken, including the time of the injury, the mechanism of the injury (rear impact, direct collision, impact from the side of the car), position in the vehicle during the accident (driver, front passenger, back seat), use of seat belt, the VAS (22,23). After that, a physical examination and radiological examination including anterior-posterior X-ray of the cervical spine (AP), lateral and functional images, were performed in accordance with the Canadian cervical spine rule (24).

**Intervention.** After the examination, all patients were recommended to rest, start with active stretching exercises of the neck muscles as early as possible, topical use of a gel containing dexketoprofen 3 times a day, and use of NSAIDs as needed.

Group A received a recommendation to use diazepam 5 mg tablets once a day (at bedtime) for the first seven days after the injury, after which it should have been discontinued. Group B (control group) did not receive a recommendation for the use of diazepam in the therapy.

## Methods

**Data collection tool.** Three previously validated scales were used: Visual Analogue Pain Scale (VAS) was used to evaluate neck pain intensity, and it rated pain from 0 to 10 (25); Neck Disability Index (NDI) was used to determine the severity of cervical spine problems (26)**;** and Whiplash Disability Questionnaire (WDQ), which is a 13-item questionnaire that quantifies cervical spine problems caused by whiplash and ranges from 0 (no difficulties) to 10 (expressed difficulties) (27).

**Subsequent assessments**. At the first follow-up, 7 days after the initial examination, VAS score was measured again. In addition, the patients were given two questionnaires, NDI and WDQ, that were completed in the office after the examination.

At the subsequent follow-up examination, 6 weeks after the initial examination, the VAS score, NDI, and WDQ scores were measured. At the last follow-up examination, 6 months after the initial examination, VAS score, NDI, and WDQ scores were measured again.

**Outcome measurement**. The primary outcome of this study was a change in the NDI score and WDQ score 6 months after the injury. These scores were compared to the same scores at the first follow-up examination 7 days after the injury.

Secondary outcomes included changes in VAS scores 7 days, 6 weeks, and 6 months after the injury; changes in NDI and WDQ scores on the second follow-up examination (after 6 weeks).

## Statistical analysis

According to the Shapiro-Wilk test, the distribution of the data was found non-normal. The sig-

nificance of categorical variables in both groups was tested using the $\chi 2$ test. The Mann-Whitney U test was used to determine the difference between the two groups. The VAS, WDQ, and NDI values in two patient groups were compared using the Kruskal-Wallis test. A $p<0.05$ was regarded as significant.

## RESULTS

Data analyses of 89 individuals were performed, 46 (51.7%) were allocated to the control group, and 43 (48.3%) were assigned to the study group (who used diazepam 5 mg once per day) (p=0.750); 50 (56.2%) were males, and 39 (43.8%) were females. In the control group, 30 males and 16 females were recruited, whereas the number of males and females in the study group was 20 and 23, respectively. However, no significant differences were observed among genders in both groups. Overall mean age was 34.80±12.531 years (minimum 19, maximum 68).

**Table 1. Demographic characteristics of the control and diazepam groups**

| Variable | Total | Control group | Diazepam group | p |
|---|---|---|---|---|
| **Gender** (No) | | | | |
| Male | 50 | 30 | 20 | 0.076 |
| Female | 39 | 16 | 23 | |
| **Total** | 89 | 46 | 43 | 0.750 |
| **Mean age** (±SD) (years) | 34.80 ±12.531 | 34.48 ±13.363 | 35.14±11.724 | 0.527 |
| **Age group** (years) (No) | | | | |
| 18-30 | 38 | 18 | 20 | 0.197 |
| 31- 40 | 23 | 16 | 7 | |
| 41 -50 | 14 | 5 | 9 | |
| >51 | 14 | 7 | 7 | |

The test revealed no significant differences in VAS score at different intervals. Initially, median of VAS score in the control group (n= 46) was 5 (mean =5.37) and in the study group (n= 43), median was 6 (mean =5.93) (p=0.248). On the first follow-up examination 7 days after the initial examination, VAS score median in the control group was 5 (mean =5.26) and in the study group 5 (mean =5.23) (p=0.828). On the follow-up examination 6 weeks after the initial examination, the median VAS score in the control group was 2 (mean =2.39) and in the study group it was 2 (mean =2.26) (p=0.707). Six months after the initial examination median VAS score in the control group was 0 (mean =0.54) and in the study group it was 0 (mean =0.49) (p=0.688). No significant difference was found at any stage between the study group and the control group (p>0.05) (Table 2).

**Table 2. Visual Analogue Scale (VAS) score at different intervals in the control and diazepam groups**

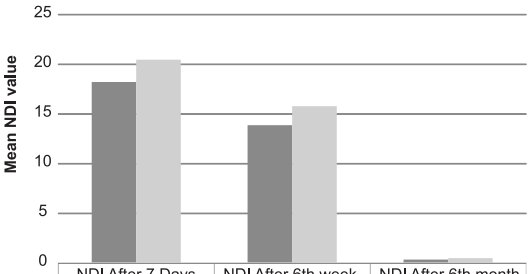
| Time interval | VAS score | | | | | p |
|---|---|---|---|---|---|---|
| | Mean rank score | | Mean | Minimum | Maximum | |
| | Control Group | Study Group | | | | |
| Initially | 41.97 | 48.24 | 5.64 | 2 | 10 | 0.248 |
| After 7 days | 45.57 | 44.40 | 5.25 | 0 | 9 | 0.828 |
| After 6 weeks | 45.98 | 43.95 | 2.33 | 0 | 6 | 0.707 |
| After 6 months | 45.88 | 44.06 | 0.52 | 0 | 3 | 0.688 |

The mean value of WDQ in the control group was 52.02±25.187, 53.57±56.592 and 1.00±2.160, 7 days, 6 weeks and 6 months after the initial examination, respectively; in the study group, it was 62.95±31.58, 52.44±29.36 and 1.09±2.021, respectively. No significant difference between the two groups was observed at any point (p>0.05) (Table 3).

**Table 3. Association of the Whiplash Disability Questionnaire values in the study and control groups**

| Time period | Whiplash Disability Questionnaire (Mean±SD) | | | p |
|---|---|---|---|---|
| | Control group | Study group | Mean (both groups) | |
| **Day 7** | 52.02±25.187 | 62.95±31.58 | 57.30 ± 28.822 | 0.062 |
| **6 weeks** | 53.57±56.592 | 52.44±29.36 | 53.02 ± 45.273 | 0.316 |
| **6 months** | 1.00±2.160 | 1.09±2.021 | 1.04 ± 2.083 | 0.559 |

There was no significant difference in the NDI scores between the two groups after six weeks (p=0.438) and six months (p=0.183) (Figure 1).




| | NDI After 7 Days | NDI After 6th week | NDI After 6th month |
|---|---|---|---|
| Control Group | 18.22 | 13.87 | 0.35 |
| Study Group | 20.47 | 15.79 | 0.49 |

**Figure 1. Mean value of the Neck Disability Index (NDI) in the study and control groups**

## DISCUSSION

The current randomized controlled study was performed to investigate the role of diazepam therapy on the long-term functional outcome of whiplash injury. The results showed that the role of diazepam in relieving neck pain was not significant.

At the 6-week follow-up examination, a significant decrease in VAS score, WDQ score, and NDI was observed in both groups compared to the first follow-up examination 7 days after the injury without significant difference between the two groups.

In our study, similar findings were observed on the follow-up examination after 6 months when WDQ score and NDI were significantly reduced compared to the results at the follow-up examinations after 7 days and 6 weeks without significant difference between the two groups. Our results confirm findings of previous studies on the efficacy of diazepam in the treatment of low back pain (28,29).

Our findings show that the use of diazepam does not result in significant pain relief or a faster return to regular daily activities. Previous studies have also concluded that diazepam is no better than placebo when added to naproxen for acute low back pain (28,30). Moreover, the recommendations say that anti-depressants should not be used since they are ineffective in treating acute WAD (31).

Multiple studies have confirmed that neck muscles are among the injured structures in whiplash. Neck muscles are injured because of eccentric contracture, which causes them to lengthen during the contraction (32). Studies researching the level of creatine kinase after whiplash confirmed its increase in serum, but it persisted only for a short period of time (33). This normalization of creatine kinase shortly after the injury might indicate that no major muscle and neck muscle injury is the main cause of chronic neck pain after whiplash.

A study discovered that patients after whiplash could not fully relax the trapezius muscle, which can cause chronic neck symptoms. This is even further increased by guarding caused by fear of a new injury and pain (34). Another study claimed that guarding caused by fear of pain and movement after whiplash caused the decreased activity of sternocleidomastoid muscle and decreased range of motion (35).

Diazepam is associated with multiple side effects, including central nervous system and respiratory depression, dependence, and benzodiazepine withdrawal syndrome (36). Moreover, other side effects like sedation, fatigue, confusion, depression, irritability, headache, nausea etc., are also linked with whiplash injury (6,7,36). Also, the use of diazepam may aggravate headaches, nausea, fatigue etc. Other than the side effects, it also increases the financial burden (37).

The sample size of the study is a limitation. Moreover, a double-blinded study with diazepam and placebo would rule out possible bias and possible increase of symptoms regarding the expectations for higher compensation after the accident.

This is the first study assessing the role of diazepam in the management and treatment of whiplash injury and whiplash associated disorder.

In conclusion, there are no significant benefits of diazepam treatment for the management of whiplash/whiplash associated disorder. We do not advocate for using diazepam in patients who suffered whiplash injury.

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## TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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